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O.I.P.E. CLASSIFIER			8-23-00
FORMALITY REVIEW		68108	11-7-00
RESPONSE FORMALITY REVIEW			



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Bib Data Sheet

SERIAL NUMBER 60/224,396	FILING DATE 08/10/2000 RULE -	CLASS -	GROUP ART UNIT -	ATTORNEY DOCKET NO. -
APPLICANTS Thomas L. Cantor, Santee, CA ; ** CONTINUING DATA ***** ** FOREIGN APPLICATIONS *****				
IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 11/01/2000				
Foreign Priority claimed <input type="checkbox"/> yes <input type="checkbox"/> no 35 USC 119 (a-d) conditions <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> Met after met Allowance Verified and Acknowledged <u> </u> Examiner's Signature Initials		STATE OR COUNTRY CA	SHEETS DRAWING 1	TOTAL CLAIMS -
INDEPENDENT CLAIMS -				
ADDRESS Brian D Voyce Suite C204 1100 Possum Trot Road North Myrtle Beach ,SC 29582				
TITLE Parathyroid hormone agonists and abnormal cyclase inhibiting parathyroid Hormone activity				
FILING FEE RECEIVED 75	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit	

PATENT APPLICATION SERIAL NO. _____

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FEE RECORD SHEET

06/13/2000 AGGITCH 00000058 60244356

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PTO-1556
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U.S. GPO: 1989-459-707/18144

08-11-00

H/PRO

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JCS97 U.S. PTO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Request for Filing a Provisional Patent Application
Cover Sheet (37 CFR 1.53(c))

JCS41 U.S. PTO
60/224396
08/10/00

Assistant Commissioner for Patents
Washington, D. C. 20231

BOX PROVISIONAL APPLICATION

Sir:

Enclosed for filing is the following provisional utility patent application:

Inventors: Thomas L. Cantor

For: "Parathyroid Hormone Agonists and Abnormal Cyclase Inhibiting Parathyroid Hormone Activity"

(The invention claimed is not made by a United States Government agency or under contract with such an agency.)

Also enclosed are:

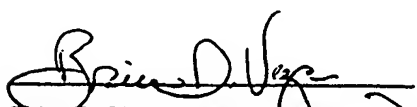
- ☒ _____ sheets of drawing(s)
- ☒ Sequence Listing & ☒ Diskette
- ☒ Declaration by Inventors
- ☒ Small Business Entity Status Declaration

Small B/S

BASIC FEE----- Small entity ----- \$75.00

☒ A check in the amount of \$75.00 to cover the filing fee is enclosed.

Respectfully submitted,


Brian D. Voyce, Reg. No. 28,917

1100 Possum Trot Road, Suite C204
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843-272-1471

SMALL ENTITY STATUS DECLARATION

I declare that I am an officer of Scantibodies Laboratory, Inc., a small business concern having its principal place of business at 9336 Abraham Way, Santee, California, and that I am empowered to sign this document.

I also declare that Scantibodies Laboratory, Inc., qualifies as a small business concern as defined in 37 CFR 1.9(d), i.e., it and all its affiliates employ no more than 500 employees as an average over the previous fiscal year, including full-time or temporary employees.

I also declare that all rights, title, and interest to the invention in a patent specification entitled as "*Parathyroid Hormone Agonists and Abnormal Cyclase Inhibiting Parathyroid Hormone Activity*", by inventor Thomas L. Cantor, have been exclusively assigned to Scantibodies Laboratory, Inc.

I acknowledge the duty to file any change of status with the Commissioner of Patents and Trademarks before paying any issue or maintenance fee.

I declare that all statements made herein of my own information, knowledge or belief are believed to be true. I acknowledge that any willful, false statements made herein are punishable by fine or imprisonment, or both under 18 USC 1001. Such statements may jeopardize the validity of any patent application or patent related thereto.



(Thomas L. Cantor)

President - SCANTIBODIES LABORATORY, INC.

August 10, 2000

08/10/00
JC897 U.S. PTO

SEQUENCE LISTING

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Glu Lys Ser Leu Gly Glu Ala Asn Lys Ala Asp Val Asn Val Leu

35 40 45

Thyr Lys Ala Lys Ser Gln

50

PARATHYROID HORMONE AGONISTS AND ABNORMAL CYCLASE INHIBITING PARATHYROID HORMONE ACTIVITY

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TECHNICAL FIELD

10 The present invention relates to the novel use of parathyroid hormone (PTH) agonists to treat abnormal cyclase inhibiting PTH activity. In particular, parathyroid hormone agonists (cyclase activating PTH, cyclase activating PTH agonist/analogue peptides, calcilytic agents, circulatory calcium lowering agents, or conservatively substituted variants thereof exhibiting PTH agonist activity and a pharmaceutical carrier or excipient) are administered to a patient having an elevated cyclase inhibiting PTH level. The administration of these agonists will modulate down the net effect of cyclase inhibiting PTH, thereby assisting in the treatment for soft tissue calcification or abnormal metabolic bone disease.

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BACKGROUND ART

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Calcium plays an indispensable role in cell permeability, the formation of bones and teeth, blood coagulation, transmission of nerve impulse, and normal muscle contraction. The concentration of calcium ions in the blood is, along with calcitriol and calcitonin, regulated mainly by parathyroid hormone (PTH). Extracellular calcium levels are directly affected by PTH through calcium uptake in kidney tubule cells and calcium transport to or from bone. Although calcium intake and excretion may vary, PTH serves through a feedback mechanism to maintain a steady concentration of calcium in cells and surrounding fluids. When serum calcium lowers, the parathyroid glands secrete PTH, affecting the release of stored calcium. When serum calcium increases, stored calcium release is retarded through lowered secretions of PTH.

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30

The complete or whole form of human PTH, (hPTH), is a unique 84 amino acid peptide (SEQ ID NO. 1), as is shown in FIGURE 1. Researchers have found that this peptide has an anabolic effect on bone that involves a domain for protein kinase C activation (amino acid residues 28 to 34) as well as a domain for adenylate cyclase activation (amino acid residues 1 to 7). However, various catabolic forms of clipped or fragmented PTH peptides also are found in circulation, most likely formed by intraglandular or peripheral metabolism. For example, hPTH can be cleaved between amino acids 34 and 35 to produce a (1-34) PTH N-terminal fragment and a (35-84) PTH C-terminal fragment. Likewise, clipping can occur between either amino acids 36 and 37 or 37 and 38. Recently, a large PTH fragment referred to as "non-(1-84) PTH" has been disclosed which is clipped closer to the N-terminal end of PTH. (See R. LePage *et alia*, "A non-(1-84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic samples " Clin Chem (1998); 44: 805-810.)

PTH plays a role in the course of disease in a patient with chronic renal failure. Renal osteodystrophy (RO) is a complex skeletal disease comprising osteitis fibrosa cystica (caused by PTH excess), osteomalacia, resulting in unmineralized bone matrix (caused by vitamin D deficiency), extraskletal calcification/ossification (caused by abnormal calcium and phosphorus metabolism), and adynamic bone disease (contributed to by PTH suppression). Chronic renal failure patients can develop RO. Failing kidneys increase serum phosphorus (hyperphosphoremia) and decrease 1,25-dihydroxyvitamin D (1,25-D) production by the kidney. The former results in secondary hyperparathyroidism from decreased gastrointestinal calcium absorption and osteitis fibrosa cystica from increased PTH in response to an increase in serum phosphorus. The later causes hypocalcemia and osteomalacia. With the onset of secondary hyperparathyroidism, the parathyroid gland becomes less responsive to its hormonal regulators because of decreased expression of its calcium and vitamin D receptors. Serum calcium drops. RO can lead to digital gangrene, bone pain, bone fractures, and muscle weakness.

To treat secondary hyperparathyroidism, patients are given calcium and vitamin D analogues. Vitamin D analogues, such as calcitriol, stimulate intestinal calcium transport, calcium absorption in bone and calcium tubular reabsorption in kidneys. Such therapy has its dangers. Serum calcium levels must be carefully monitored. Too much dosage can induce hypercalcemia or hypercalciuria, leading to the onset of adynamic low bone turnover disease. There are serious consequences to the patient from the mismanagement of calcium levels by either direct or indirect PTH suppression therapy. Soft tissue calcification has led to a five to fifteen times greater incidence of myocardial infarction among end stage renal dialysis patients compared to age matched diabetes patients. The secondarily hyperplastic parathyroid glands escape PTH control over calcium, a condition referred to as tertiary hyperparathyroidism.

DISCLOSURE OF THE INVENTION

The present invention relates to the novel use of parathyroid hormone (PTH) agonists to treat abnormal cyclase inhibiting activity. In particular, parathyroid hormone agonists (cyclase activating PTH, cyclase activating PTH agonist/anologue peptides, calcilytic agents, circulatory calcium lowering agents such as EDTA, oxalate salts or citrate salts, or conservatively substituted variants thereof exhibiting PTH secretion stimulation or PTH agonist activity and a pharmaceutical carrier or excipient) are administered to a patient having an elevated cyclase inhibiting PTH level. The administration of these agonists will modulate down the net biological effect of cyclase inhibiting PTH, thereby assisting in the treatment for soft tissue calcification or abnormal metabolic bone disease.

Cyclase inhibiting PTH (CIP) is a natural peptide (from PTH₂₋₄₄ SEQUENCE ID NO. 3 to PTH₃₄₋₄₄ SEQUENCE ID NO. 4) found in a human along with cyclase activating PTH (CAP) (PTH₁₋₄₄ SEQUENCE ID NO. 1). For people with normal bone metabolism, it has been found typically that CAP levels are less than about 40 and CIP levels are less

than about 30 wherein the CAP/CIP ratio is greater than one. However, people with an abnormal bone metabolism have a CAP level greater than about 100 and a CIP level of over 100. Also, it has been found that to identify patients with abnormal CIP activity, the patient has a ratio of CAP level to CIP level that is typically less than 1. Thus, for the purposes of this invention, an abnormal CIP activity includes persons having an elevated CIP level, especially in comparison to CAP levels, that leads to a clinical significance of abnormal bone metabolic disease, (as typified by adynamic low bone turnover and a CAP to CIP ratio of less than one) and soft tissue calcification. Quite often, abnormal CIP activity is found in renal failure patients on dialysis with low bone turnover disease.

To determine whether or not a patient has abnormal CIP activity, one should measure the CAP level and CIP level. Such serum measurements can be made using assays available from Scantibodies Laboratory, Inc. of Santee, California. One should not use either conventional "intact" PTH or "total" PTH assays to make this determination. To do so would be to measure a diagnostically inferior combination of CAP and CIP together. One must use assays that can distinguish between CAP and either CIP alone or a true total PTH assay of CAP and CIP, (calculating the CIP level by subtraction.) For example, it has been unexpectedly found that some renal failure patients with bone biopsy confirmed adynamic low bone turnover disease have a high "intact" PTH level (2200 pg/ml) that is almost entirely CIP (only 20 pg/ml CAP).

Having determined that a patient has a CAP level greater than about 100, a CIP level of over 100, and preferably a ratio of CAP level to CIP level of less than 1, one can proceed with administering PTH agonists or PTH secretion stimulating agents, preferably CAP, as proper therapeutic agents.

A person having abnormal CIP activity has too much CIP present, inhibiting the biological effect of CAP. Proper treatment for such people is to administer not the conventional CAP suppressant treatment (vitamin D analogues, calcium, calcimimetics, or parathyroidectomy) as could be mistakenly done under prior regimens using "intact" PTH

measurements, but rather to follow the exact opposite therapeutic strategy and to administer PTH agonists. For the purposes of this invention, PTH agonists include CAP, CAP agonist peptides, calcilytic agents, circulatory calcium lowering or PTH secretion stimulating agents (such as EDTA, citrate salts, or oxalate salts) or conservatively substituted variants thereof exhibiting PTH agonist activity. CAP agonists include CAP peptides having an amino acid sequence from between SEQ ID No. 1 [PTH₁₋₃₄] and SEQ ID No. 2 [PTH₁₋₃₄].

PTH agonists useful in the present invention exhibit both oral and parenteral activity and can be formulated in solid or liquid dosage forms for oral, parenteral, intranasal, topical, or injectable administration using known carriers, excipients, or the like. The exact amount of present PTH agonist used can vary depending upon the degree of agonist property desired, the route of administration, or the duration of the treatment, as is known to the art. Many methods of administration for such components are known, including pulsatile administration, nasal inhalation, injection, or the like. In all cases, the PTH agonists should be used in a therapeutically effective, but non-toxic amount.

It should be noted that the use of conventional PTH assays, such as "intact" PTH assays, are not suitable for use in the present invention. The use of such assays is misleading to the physician, in that one is measuring a mixture of CAP and CIP with such assays. One needs to use assays that accurately measure and differentiate between CAP and CIP, so that one can assess whether or not a patient has an abnormal CIP level.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a diagrammatic view of hPTH.

BEST MODES FOR CARRYING OUT THE INVENTION

In disclosing the present invention, one should remember that there are a number of
5 closely analogous, species dependent forms of PTH. The amino acid sequence of hPTH is
shown in FIGURE 1. However, for rat PTH, bovine PTH, or porcine PTH, for example,
one finds the substitutions at some of the amino acids in the hPTH sequence. For the
purposes of the present invention, one can use interchangeably forms of these PTH's,
although it is preferred to use a PTH having a sequence matching the species in which the
10 PTH antagonist is used.

Surprisingly, adynamic low bone turnover has been found in humans with an
elevated intact PTH level. Unexpectedly, the true nature of these patients is a CAP to CIP
ratio of less than 1. In such cases, one should stop PTH suppression therapy called for by
15 the elevated intact PTH levels and instead administer PTH agonists in accordance with the
present invention. Twenty-eight chronically dialyzed patients with low bone turnover as
measured by bone biopsy were tested for their CAP to CIP ratio. In all cases this ratio was
less than 1. In one case the CAP level was 20 pg/ml while the CIP was 2200 pg/ml. With
normal therapy, this patient could have been a candidate for removal of the parathyroid
20 gland, the exact opposite of the treatment the patient needs according to the present
invention.

PTH agonist peptide preparation

In order to make the present compositions, one can use any conventionally known
25 method. For example, one can use recombinant DNA methods to produce the desired
compound.

Alternatively, one can use an automated peptide synthesizer, such as Model 431
made by Applied Biosystems, Inc. (Foster City, California, U.S.A.) Fmoc (9-
30 fluoronylmethoxycarbonyl) can be used as the alpha-amino protecting group. All amino

acids and solvents are available from Applied Biosystems and are of synthesis grade. Following synthesis, the peptide is cleaved from the resin, and side chains are de-blocked, using a cleavage cocktail containing 6.67% phenol, 4.4% (v/v) thioanisole and 8.8% ethanedithiol in trifluoroacetic acid (TFA). The cleaved peptide is precipitated and washed several times in cold diethyl ether. It is then dissolved in water and lyophilized. The crude peptide is subjected to amino acid analysis (Waters PICO-TAG System, Boston, Massachusetts, U.S.A.) and reversed-phase HPLC using a VYDAC (TM) C8 column with 0.1% TFA in water and 99.9% acetonitrile in 0.1% TFA as the mobile buffers. The presence of a single major peak along with the appropriate amino acid composition is taken as evidence that the peptide is suitable for further use.

PTH Pharmaceutical compositions

The present PTH agonist peptides exhibit both oral and parenteral activity and can be formulated in solid or liquid dosage forms for oral, parenteral, intranasal, topical, or injectable administration using known carriers, excipients, or the like. The exact amount of present PTH agonist used can vary depending upon the degree of agonist property desired, the route of administration, or the duration of the treatment, as is known to the art.

Agonist Properties

The present PTH agonists have the ability to increase serum calcium in the presence of abnormal levels of CIP. FIGURE 2 is a graph demonstrating such a property. Twenty-five rats were used in a demonstration of the effect of the present PTH agonists. All of the rats had their parathyroid glands removed. Five rats received an *i.v.* injection of a saline control. The serum calcium of the control rats was measured and on average was lowered over time by about 0.18 mg/dl. Nine rats received an *i.v.* injection (10 µg/kg) of hPTH obtained from Bachem, AG of Bubendorf, Switzerland. The serum calcium of the hPTH rats was measured and on average was raised by about 0.65 mg/dl. Five rats received an equimolar *i.v.* injection of a PTH₇₋₈₄ also obtained from Bachem, AG of Bubendorf, Switzerland. The serum calcium of the PTH antagonist rats was measured and on average was lowered over time by about 0.30 mg/dl. Finally, six rats received an *i.v.* injection

comprised of hPTH (10 μ g/kg) and an equimolar amount of PTH₇₋₄₄. The serum calcium of the hPTH/PTH antagonist rats was measured and on average remained substantially the same, raising only about 0.03 mg/dl. Thus, a PTH agonist was able to prevent the substantial serum calcium decrease normally associated with abnormal levels of CIP.

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The ordinarily skilled artisan can appreciate that the present invention can incorporate any number of the preferred features described above.

10 All publications or unpublished patent applications mentioned herein are hereby incorporated by reference thereto.

15 Other embodiments of the present invention are not presented here which are obvious to those of ordinary skill in the art, now or during the term of any patent issuing from this patent specification, and thus, are within the spirit and scope of the present invention.

WE CLAIM:

1. A method for treating a patient having abnormal cyclase inhibiting parathyroid hormone (CIP) activity comprising administering to the patient a cyclase activating parathyroid hormone (CAP) peptide having an amino acid sequence from between (SEQ ID No. 1 [PTH₁₋₄₄]) and (SEQ ID No. 2 [PTH₁₋₃₄]) or a conservatively substituted variant thereof exhibiting parathyroid hormone (PTH) agonist activity in a therapeutically effective, but non-toxic amount.
2. The method of Claim 1 wherein the patient has a ratio of CAP to CIP of less than one to one.
3. The method of Claim 1 wherein one determines the amount of CAP and CIP present in the patient.
4. A method for treating a patient having abnormal cyclase inhibiting parathyroid hormone (CIP) activity comprising administering to the patient a calcilytic agent in a therapeutically effective, but non-toxic amount, thereby stimulating the natural patient production of cyclase activating parathyroid hormone (CAP).
5. The method of Claim 4 wherein the patient has a ratio of CAP to CIP of less than one to one.
6. The method of Claim 4 wherein one determines the amount of CAP and CIP present in the patient.
7. A method for treating a patient having abnormal cyclase inhibiting parathyroid hormone (CIP) activity comprising administering to the patient a parathyroid hormone secretion stimulating agent in a therapeutically effective, but non-toxic amount, thereby stimulating

8. The method of Claim 7 wherein the patient has a ratio of CAP to CIP of less than one to one.

9. The method of Claim 7 wherein one determines the amount of CAP and CIP present in the patient.

10. The method of Claim 7 wherein the parathyroid hormone secretion stimulating agent is selected from the group consisting of oxalates, citrates, phosphates, or chelating agents.

00000000

15

ABSTRACT

The present invention relates to the novel use of parathyroid hormone (PTH) agonists to treat abnormal cyclase inhibiting PTH activity. In particular, parathyroid
5 hormone agonists (cyclase activating PTH, cyclase activating PTH agonist/analogue peptides, calcilytic agents, circulatory calcium lowering agents, or conservatively substituted variants thereof exhibiting PTH agonist activity and a pharmaceutical carrier or excipient) are administered to a patient having an elevated cyclase inhibiting PTH level. The administration of these agonists will modulate down the net biological effect of cyclase
10 inhibiting PTH, thereby assisting in the treatment for soft tissue calcification or abnormal bone metabolic disease, especially adynamic low bone turnover disease.

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Sent By: VOYCE;

SCANTIBODIES LAB

843 272 1471;

+ BRIAN VOYCE

Aug-9-00 23:08;

009/010
Page 8/13

**U. S. PATENT APPLICATION SOLE
DECLARATION AND POWER OF ATTORNEY
37 CFR 1.63**

As a below-named sole inventor, I hereby declare that:

My individual residence, post office address, and citizenship is as stated below next to my name. I believe that I am the original and first sole inventor of the subject matter claimed in the patent application entitled: "*Parathyroid Hormone Agonists and Abnormal Cyclase Inhibiting Parathyroid Hormone Activity*", which was filed concurrently herewith.

Acknowledgment of Review of Papers and Duty of Candor

I have reviewed and understand the above-identified patent application, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this specification pursuant to 37 CFR Section 1.56(a).

Power of Attorney

I appoint Brian D. Joyce, a registered patent attorney, to prosecute this patent application and to transact all business associated therewith in the U. S. Patent and Trademark Office.

Address

Telephone Number

1100 Possum Trot Road, Suite C204
North Myrtle Beach, SC 29582

843-272-1471

I declare that all statements made herein are of my own knowledge, information, or belief and are believed to be true; these statements being made with the knowledge that willful false statements are punishable under 18 USC Section 1001 by fine or imprisonment and may jeopardize the validity of this patent application or any patents issued therefrom.


Thomas L. Cantor - Inventor

August 10, 2000

Country of Citizenship - U. S. A.

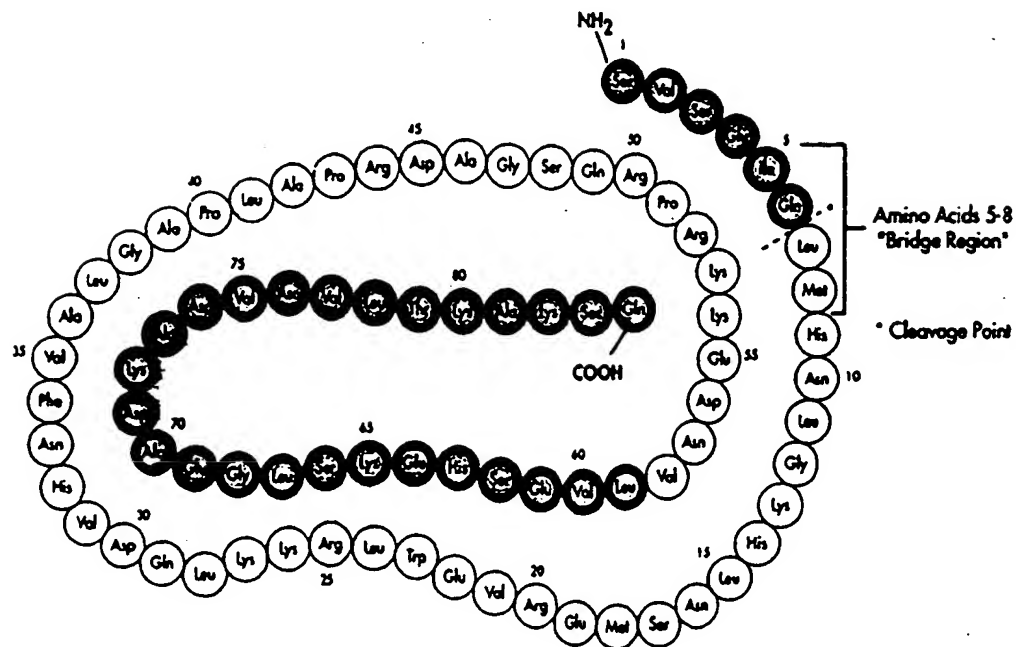
Residence - 11149 Shining Light Way
El Cajon, CA 92020

Postal Address - Same as Residence

0001000-0010000

FIG. 1

Whole Human PTH (1-84)



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001

Luco Forward et. al. 11/21 1 11:28 PAGE 3/3 RIG FAX

IN UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of Thomas L. CANTOR
Serial No.: 60/224,396
Filed: August 10, 2000
Title: "Parathyroid Hormone Antagonists and Abnormal Cyclase Inhibiting
Parathyroid Hormone Activity."


POWER TO INSPECT

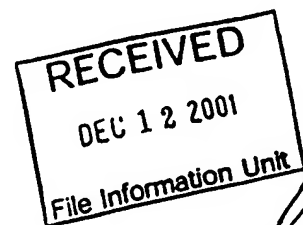
Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

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Dated: 21 Nov 2001


Thomas L. Cantor
Inventor



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